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Attempted Resolution of Free (±)-Chlorophenylisopropylphosphine

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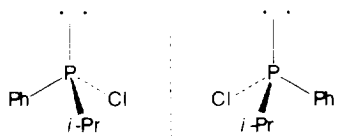
Abstract: (±)-Chlorophenylisopropylphosphine has been resolved in a palladium(II) complex containing the phosphine and ortho-metalated (*R*)-1-[1-(dimethylamino)ethyl]naphthalene; the configurationally homogeneous (*R*,*R*p) diastereomer of the complex crystallises from the reaction mixture by typical second-order asymmetric transformation in overall 82% yield. The absolute configuration of the complex was determined by X-ray crystallography. The pure (*R*,*R*p) diastereomer of the complex reacts quantitatively with methanol in the presence of triethylamine to give the corresponding methoxyphosphine complex with complete stereoselectivity and inversion at phosphorus. All attempts at liberating optically active chlorophosphine from the palladium complex were unsuccessful.

Although calculations indicate substantial pyramidal stability at phosphorus in halophosphines of the type (±)-PXR^1R^2,[1] little work has been published on the resolution of such compounds. The first reported attempts at synthesising optically active fluoro- and chloro-phosphines from optically active compounds of the type $P(NR_2)R^1R^2$ by cleavage of the amino group with acyl halides, hydrogen chloride, or phosphorus trichloride, were unsuccessful,[2] but the conversion of (*S*)-(−)-[P(SMe)Cl(*t*-Bu)Ph]CF_3SO_3 of 63% optical purity into (*S*)-(+)-PCl(*t*-Bu)Ph of 49.4% optical purity by desulfurisation with $P(NMe_2)_3$ at −70 °C, was reported in 1992.[3] The chlorophosphine lost its optical activity over 20 h in the polarimeter cell (conditions not specified). In recent work, we have shown that (±)-PFPh(*i*-Pr), although readily decomposing into PF_3Ph(*i*-Pr) and Ph(*i*-Pr)P–PPh(*i*-Pr) by equilibrium redox disproportionation, can be resolved in a palladium(II) complex containing ortho-metalated (*R*)-1-[1-(dimethylamino)ethyl]naphthalene, and from which optically pure (*S*)-(−)-PFPh(*i*-Pr) can be liberated.[4] The substitution of the fluoride by methoxide in the fluorophosphine palladium complex proceeds with predominant inversion at phosphorus.[4b] We have also shown that (±)-PClMePh and (±)-AsFMePh can be resolved in certain kinetically stable iron(II) complexes.[5] Here we report that (±)-PClPh(*i*-Pr) can be resolved in a palladium(II) complex containing ortho-metalated (*R*)-1-[1-(dimethylamino)ethyl]naphthalene and that substitution of chloride by methoxide in a configurationally homogeneous diastereomer of the complex proceeds with complete inversion at phosphorus to give the corresponding methoxyphosphine complex with high stereoselectivity. The chiral chlorophosphine could not be liberated from the configurationally pure complex in optically active form.

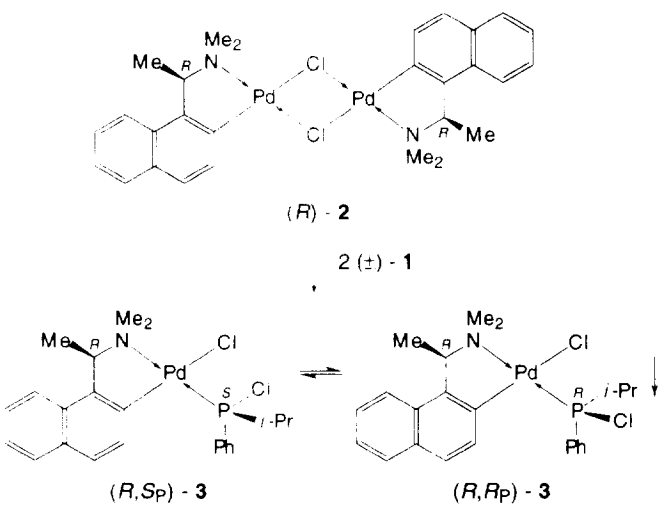


(*R*)-**1** (*S*)-**1**

Results and Discussion

The reaction of 2 equiv. (±)-PClPh(*i*-Pr), (±)-**1**,[6] with (*R*)-**2**·CH_2Cl_2[7] in dichloromethane produces the pair of diastereomeric complexes (*R*,*R*P)- and (*R*,*S*P)-**3** in unequal amounts, as evidenced in the $^{31}P\{^1H\}$ NMR spectrum of the reaction mixture by the two singlets for the diastereomers at δP 119.32 and 134.02 ppm having the ratio of 22/78, respectively (Scheme 1). No change in the diastereomeric ratio was observed over several days. Removal of the solvent from the reaction mixture in vacuo, followed by treatment of the residue with diethyl ether, afforded a crystalline product that was filtered off and dried. The $^{31}P\{^1H\}$ NMR spectrum of this less-soluble fraction exhibited the singlets at δP 134.02 and 119.32 ppm in the enriched ratio of 95/5; the spectrum of the mother liquor had δP(134.02)/δP(119.32) = 87/13. Recrystallisation of the solid from dichloromethane–diethyl ether afforded the diastereomer with δP 134.02 ppm as colourless prisms in ≥ 99% purity. Three additional fractions of similar purity were obtained by work-up of the mother liquor: the combined yield of the diastereomer having δP 134.02 ppm was 82%. The mother liquor from the final crystallisation from dichloromethane–diethyl ether contained both diastereomers in the ratio 82/18. It is noteworthy that the position of the equilibrium between the diastereomeric palladium(II) complexes depends upon the nature of the solvent: in dichloromethane the ratio is 78/22, in dichloromethane–benzene (1/1) it is 81/19, in dichloromethane–diethyl ether (1/8) it is 82/18, and in diethyl ether it is 87/13. Thus, the crystallisation of the single diastereomer from dichloromethane–diethyl ether proceeds by second-order asymmetric transformation.[8] The diastereomer having δP 134.02 ppm is kinetically labile in dichloromethane-d_2 and epimerises into the equilibrium 78/22 mixture of diastereomers over 19 days. This behaviour contrasts with that of the corresponding fluorophosphine complex.[4] The interconversion between (*R*,*R*P)- and (*R*,*S*P)-**3** could be due to ligand dissociation, or exchange involving traces of free (±)-**1** with one or both of the diastereomers, with subsequent racemisation of the free phosphine by halide exchange (via cationic phosphorus intermediates[9,10]) and recoordination.

The diastereomer having δP 134.02 ppm was identified as (*R*,*R*P)-**3** by X-ray crystallography. Crystal data are listed in Table 1 and an ORTEP plot of the molecule is given in Figure 1. The P–Cl distance in



Scheme 1

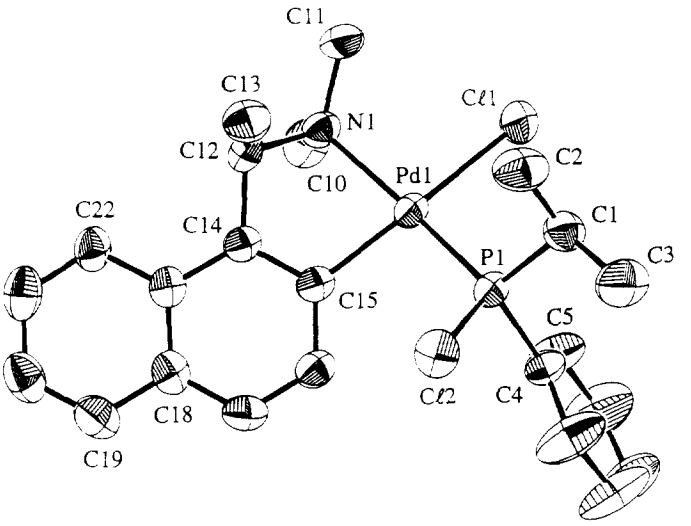
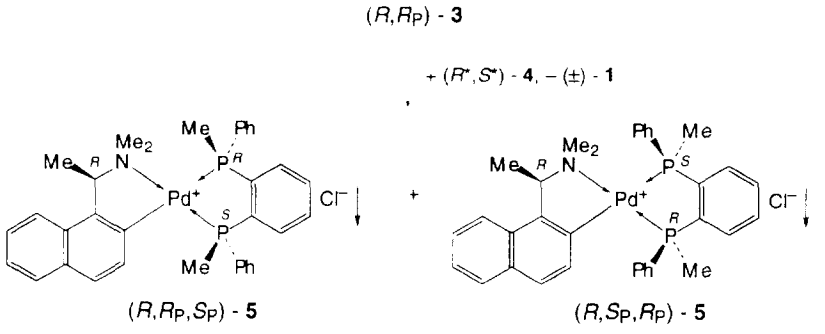


Fig. 1 ORTEP drawing of (*R*,*R*P)-**3**. Selected interatomic distances (Å) and angles (°) are as follows: Pd1–P1 2.229(1), Pd1–Cl1 2.394(1), Pd1–N1 2.142(4), Pd1–C15 1.998(4), P1–Cl2 2.041(2), P1–C1 1.818(5), P1–C4 1.816(4), P1–Pd1–Cl1 91.98(5), Cl1–Pd1–N1 93.6(1), P1–Pd1–C15 95.4(1), N1–Pd1–C15 80.9(2), Cl1–Pd1–C15 168.4(1), P1–Pd1–N1 167.6(1), Pd1–P1–Cl2 115.06(7), Pd1–P1–C1 112.3(2), Pd1–P1–C4 116.7(2), Cl2–P1–C1 100.7(2), Cl2–P1–C4 102.8(2), C1–P1–C4 107.6(2).

(*R*,*R*P)-**3** is slightly shorter than similar bonds in other alkylchlorophenylphosphine complexes.[5a,11] In (*R*,*R*P)-**3**, the coordination geometry around the palladium is slightly distorted from square-planar with the phosphine ligand being situated trans to the dimethylamino group, which is typical for such complexes.[12] As is characteristic of complexes containing the ortho-palladated 1-[(1-dimethylamino)ethyl]naphthalene fragment, the benzylic methyl group avoids an unfavourable steric interaction with H22 of the naphthalene ring by adopting an axial disposition, which results in a puckered five-membered metallacycle of δ conformation.[7,12,13]

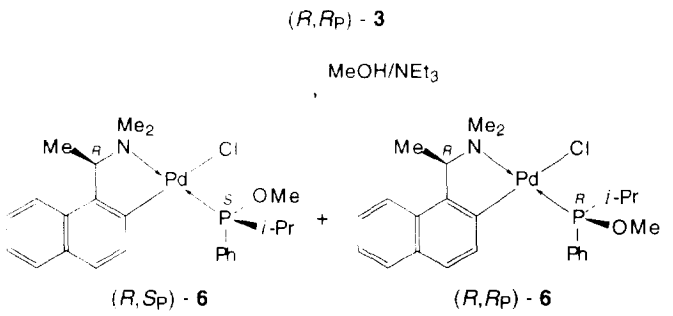


Scheme 2

The liberation of **1** from (*R*,*R*P)-**3** was accomplished by treatment of the complex with achiral (*R**,*S**)-**4**[14] in benzene-d_6 (Scheme 2). In contrast to the behaviour of the corresponding fluorophosphine,[4] however,

the displacement proceeds with complete loss of optical information at phosphorus, as verified by rapid quenching of liberated phosphine with (*R*)-**2**·CH_2Cl_2 or (*S*)-**2**·CH_2Cl_2, which in both cases afforded the expected product diastereomers in the equilibrium ratio (*R*,*R*P)-**3**/(*R*,*S*P)-**3** or (*S*,*S*P)-**3**/(*S*,*R*P)-**3** = 81/19.

Addition of (*R*,*R*P)-**3** in dichloromethane to an excess of an equimolar mixture of triethylamine and methanol led to the quantititative and completely stereoselective formation of (*R*,*S*P)-**6**,[4b] as evidenced by the singlet at δ_P 137.55 ppm in the $^{31}P\{^1H\}$ NMR spectrum of the mixture (Scheme 3). Thus, the substitution of the *P*-chloride in (*R*,*R*P)-**3** by methoxide proceeds with complete inversion at phosphorus. In other work we showed that configurationally stable (*R*)-(+)-P(OMe)Ph(*i*-Pr) can be isolated from (*R*,*S*P)-**6**·$C_6H_5CH_3$ in 92% ee by treatment of the complex with dppe.[4b]



Scheme 3

Experimental Section

Manipulations involving air-sensitive compounds were performed under a nitrogen atmosphere with use of the Schlenk technique. Diethyl ether and dichloromethane were freshly distilled from sodium benzophenone ketyl and calcium hydride, respectively, and stored under nitrogen. (±)-Chlorophenylisopropylphosphine,[6] resolving agents (*R*)- and (*S*)-**2**·CH_2Cl_2,[7] and (*R**,*S**)-1,2-C_6H_4(PMePh)$_2$ (**4**)[14] were prepared according to published procedures. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded in dichloromethane-d_2 at 23 °C on a Varian XL 200E spectrometer operating at 200.05, 50.31, and 80.98 MHz, respectively. The NMR spectra were referenced to Me_4Si (^1H, ^{13}C) or external 85% aqueous H_3PO_4 (^{31}P) with downfield shifts being positive. Optical rotations were measured in a Perkin-Elmer Model 241 polarimeter in a 1-dm cell at 20 °C. Fast atom bombardment (FAB) mass spectra were recorded on a VG Analytical ZAB-2SEQ mass spectrometer (ionization: 30 keV Cs^+ ions) in a matrix of 3-nitrobenzyl alcohol. Elemental analyses were carried out by staff within the Research School of Chemistry.

[SP-4-4]-Chloro[(R)-1-[1-(dimethylamino)ethyl]-2-naphthalenyl-C,N][(R)-chlorophenylisopropylphosphine]palladium(II) ((*R*,*R*P)-**3**). A solution of (±)-**1** (5.61 g, 30.1 mmol) in dichloromethane (100 mL) was added over 5 min to a solution of (*R*)-**2**·CH_2Cl_2 (11.40 g, 14.9 mmol) in the same solvent (350 mL). After stirring for 1 h, the solvent was removed from the reaction mixture in vacuo. Treatment of the residue with diethyl ether (50 mL) resulted in crystallisation. After stirring of the mixture for 30 min at room temperature, the crystals were filtered off, washed with diethyl ether, and dried in vacuo. The solid contained the mixture of diastereomers (*R*,*R*P)-**3**/(*R*,*S*P)-**3** in the ratio 95/5; the ratio of the corresponding diastereomers in the mother liquor was 87/13, as determined by $^{31}P\{^1H\}$ NMR spectroscopy. Recrystallisation of the solid from dichloro-

methane (25 mL) by addition of diethyl ether (200 mL) afforded (*R*,*R*P)-**3** as colourless prisms in ≥ 99% diastereomeric purity, as determined by $^{31}P\{^1H\}$ NMR spectroscopy. Three additional crystalline fractions of similar purity were obtained by removal of the solvent from the mother liquor in vacuo and by recrystallisation of the residue as described above. The final mother liquor contained (*R*,*R*P)-**3**/(*R*,*S*P)-**3** = 82/18. (*R*,*R*P)-**3**: combined yield 12.93 g (82%); mp 172 °C; $[\alpha]_D^{20}$ −102.5 (*c* 1.00, CH_2Cl_2). Anal. Calcd for $C_{23}H_{28}Cl_2NPPd$: C, 52.4; H, 5.4; Cl, 13.5; N, 2.7. Found: C, 52.1; H, 5.1; Cl, 13.2; N, 2.7. ^1H NMR: δ 0.96 (dd, ^3J(HP) = 16.0 Hz, ^3J(HH) = 10.8 Hz, 3 H, CH*Me*$_2$), 1.62 (dd, ^3J(HP) = 22.4 Hz, ^3J(HH) = 6.8 Hz, 3 H, CH*Me*$_2$), 1.98 (d, ^3J(HH) = 6.0 Hz, 3 H, CH*Me*), 2.57 (d, ^4J(HP) = 2.0 Hz, 3 H, NMe), 2.90 (d, ^4J(HP) = 4.0 Hz, 3 H, NMe), 3.34 (d of sept., ^2J(HP) = 9.2 Hz, ^3J(HH) = 6.8 Hz, 1 H, *C*HMe$_2$), 4.30 (d of quart., ^3J(HH) = 6.4 Hz ^4J(HP) = 1.2 Hz, 1 H, *C*HMe), 7.00–8.36 (m, 11 H, ArH). $^{13}C\{^1H\}$ NMR: δ 15.84 (d, ^2J(CP) = 7.0 Hz, CH*Me*$_2$), 18.94 (d, ^2J(CP) = 4.4 Hz, CH*Me*$_2$), 23.89 (s, CH*Me*), 35.79 (d, ^1J(CP) = 19.8 Hz, *C*HMe$_2$), 48.31 (d, ^3J(CP) = 2.8 Hz, NMe), 51.20 (d, ^3J(CP) = 3.4 Hz, NMe), 73.56 (d, ^3J(CP) = 3.4 Hz, *C*HMe), 123.63–152.56 (aromatics); $^{31}P\{^1H\}$ NMR: δ 134.02 (s). FAB-MS: 527.1 amu ([M$^+$]).

*Liberation of (±)-1 from (R,R*P*)-3.* Treatment of a solution of (*R*,*R*P)-**3** in benzene-d_6 with an excess of (*R**,*S**)-**4** gave a quantitative yield of (±)-**1**, as evidenced by $^{31}P\{^1H\}$ NMR spectroscopy. Quenching of the reaction mixture immediately after liberation of the halophosphine with excess (*R*)-**2**·CH_2Cl_2 or (*S*)-**2**·CH_2Cl_2 in dichloromethane led to quantitative recoordination of the chlorophosphine and afforded in both cases the expected diastereomers in the equilibrium ratio of (*R*,*R*P)-**3**/(*R*,*S*P)-**3** or (*S*,*S*P)-**3**/(*S*,*R*P)-**3** = 81/19, respectively, thus indicating complete racemisation of the free phosphine during the time taken for liberation and subsequent recoordination, viz. ca. 5 min.

*Treatment of (R,R*P*)-3 with Methanol/Triethylamine.* A solution of (*R*,*R*P)-**3** in dichloromethane-d_2 was added to a twofold excess of an equimolar mixture of methanol and triethylamine and the $^{31}P\{^1H\}$ NMR spectrum of the mixture was measured. The quantitative and stereospecific formation of (*R*,*S*P)-**6** was evidenced by the singlet at δ_P 137.55 ppm in the $^{31}P\{^1H\}$ NMR spectrum. No attempt was made to isolate the product, which has been described elsewhere.[4b]

X-Ray Crystal Structure Determination: Recrystallisation of a sample of (*R*,*R*P)-**3** from dichloromethane–diethyl ether afforded colourless prisms suitable for X-ray crystallography. Data were corrected for absorption, Lorentz-polarization, and decay (6%). The structure was solved by heavy-atom Patterson methods and expanded using Fourier techniques. Non-hydrogen atoms were refined with anisotropic displacement factors. Hydrogen atoms were included in calculated positions and were not refined. The absolute configurations were assigned on the basis of the known configuration of (*R*)-1-[1-(dimethylamino)ethyl]-naphthalene and by analysis of pairs of Friedel opposites. Data reduction was performed using Xtal[15] and for the refinement teXsan[16] was employed. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Data Centre.

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Table 1. Crystal Data and Experimental Parameters for X-ray Structure Analysis

formula	$C_{23}H_{28}Cl_2NPPd$	instrument	Philips PW1100/20
M_r	526.76	radiation	MoK_α
crystal system	orthorhombic	λ (Å)	0.71069
space group	$P2_12_12_1$ (#19)	μ (cm^{-1})	10.81
a (Å)	10.476(2)	scan mode	ω–2θ
b (Å)	11.152(2)	2θ max. for data coll. (°)	50.0
c (Å)	20.353(4)	scan angle (°)	1.20 + 0.35tanθ
cell vol. ($Å^3$)	2377(7)	no. of rflns collected	4835
Z	4	no. obs. reflns $I>3\sigma(I)$	2046
cryst dimens (mm)	0.28 × 0.18 × 0.18	no. of variables	253
d(calcd) (g cm^{-3})	1.471	temperature (K)	296
F(000)	1072	diff. Four. $\Delta\rho_{max}$ ($e^- Å^{-3}$)	0.23
R, R_w	0.025, 0.025	$\Delta\rho_{min}$ ($e^- Å^{-3}$)	-0.27
GOF	1.27		

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